

Urologic Diseases

Research Updates

National Kidney and Urologic Diseases Information Clearinghouse

Summer 2010

Low Health-related Quality of Life Found in Children with Urinary Incontinence

Urinary incontinence (UI) is common in pediatric patients with chronic kidney disease (CKD) and is associated with a lower health-related quality of life (HRQOL), as reported in the October 2009 issue of the *Journal of Urology*.

The research, funded by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and conducted by lead investigator Jennifer L. Dodson, M.D., Department of Urology, The John's Hopkins University School of Medicine, showed about 29 percent of children with CKD had UI and impaired HRQOL, which was measured using the parent and child versions of Pediatric Quality of Life (PedsQL).



Most children achieve urinary continence by age 5. Incontinence lasting longer is thought to be socially stigmatizing with negative implications on self-esteem and independence. Generally, children and adolescents with CKD have a significant disease burden and are known to have impaired HRQOL.

Dodson and colleagues set out to prove the prevalence and impact of UI on HRQOL in children with CKD enrolled in the CKiD cohort study. "We hypothesized that children with persistent incontinence after age

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The study was conducted with children enrolled in the Chronic Kidney Disease in Children Study (CKiD). CKiD is a prospective, observational cohort of children with mild to moderate CKD and is funded by the National Institutes of Health (NIH). The study began in 2003 and will continue longitudinal follow-up through 2013.

Childhood structural urological disease is the leading cause of CKD, accounting for up to 60 percent of underlying diagnosis in the 0- to 12-year age group. "Incontinence and delayed toilet training are common in children with structural urological disease and may disproportionately affect HRQOL," Dodson and colleagues wrote.

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"Although the symptom of urinary incontinence is common in patients with CKD and often treated by urologists, assessing its impact on the life of the child or adolescent is not often quantified from the child point of view or by parent proxy."

Jennifer L. Dodson, M.D.
Department of Urology, The John's Hopkins University School of Medicine, and colleagues

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5 years would have worse generic HRQOL on PedsQL than those with normal continence," Dodson stated.

The study group consisted of 329 participants ages 5 to 16, with a median age of 12.5 years. Continence status was ascertained from a parent-completed questionnaire, HRQOL was measured using PedsQL child and parent reports, and the study was adjusted for demographic variables.

Overall, 55.5 percent of children had a urological diagnosis, with most cases being obstructive uropathy (34.8 percent), reflux nephropathy (28.2 percent), and aplastic/hypoplastic/dysplastic kidneys (27.1 percent). Nonurological diagnoses were present in 44.5 percent of participants, with focal segmental glomerulosclerosis being the most common cause of CKD (17 percent) in children.

Researchers found that the PedsQL scores for children had diminishing HRQOL as the level of incontinence worsened from toilet trained to bedwetting to not toilet trained. Parent PedsQL scores regarding HRQOL and level of incontinence yielded similar results.

Children who were not toilet trained had a low average PedsQL total score that was statistically significant and clinically meaningful. In

bedwetting children, scores were generally between the scores of children who were and were not toilet trained.

PedsQL scores are reported in four categories: emotional functioning, physical functioning, school functioning, and social functioning. Physical functioning and school functioning were most affected from the child's perspective, while physical functioning was most affected from the parent's perspective.

Recognizing and treating incontinence may be a potentially important way to help maximize HRQOL in children with CKD. Dodson and colleagues stated, "Although the symptom of urinary incontinence is common in patients with CKD and often treated by urologists, assessing its impact on the life of the child or adolescent is not often quantified from the child point of view or by parent proxy."

The authors also assert that future longitudinal studies may inform the timing of surgical intervention for incontinence by identifying at what age surgery should be performed to help maximize HRQOL.

More information about research projects funded by the NIH can be found by using the Research Portfolio Online Reporting Tools (RePORT)

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Urologic Diseases Research Updates

Urologic Diseases Research Updates, an email newsletter, is sent to subscribers by the National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). The newsletter features news about urologic diseases, special events, patient and professional meetings, and new publications available from the NKUDIC and other organizations.

You can read or download a PDF version or subscribe to the newsletter at www.kidney.niddk.nih.gov/about/newsletter.htm.

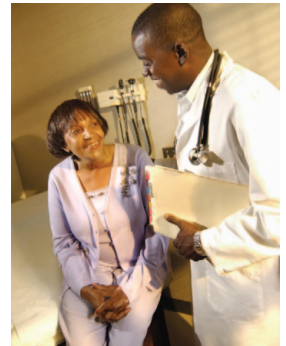
Executive Editor: Christopher Mullins, Ph.D.

Dr. Mullins serves as the director of Basic Cell Biology Programs in Urologic and Kidney Disease at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health in Bethesda, MD. Dr. Mullins is a graduate of the University of Louisville and the Vanderbilt University Graduate School of Medicine, where he completed his graduate training in the Department of Microbiology and Immunology in 1997. As a National Research Council fellow, Dr. Mullins conducted research at the Eunice Kennedy Shriver National Institute of Child Health and Human Development from 1997 to 2002 and joined the NIDDK's Division of Kidney, Urologic, and Hematologic Diseases in his present position in 2002. His responsibilities include serving as the project scientist for the NIDDK's Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network and providing development and oversight for additional NIDDK initiatives, including the NIDDK Prostate Research Strategic Plan.



Evidence Found for Overlap between Urological and Nonurological Unexplained Clinical Conditions

Researchers at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have found substantial overlap between urological and nonurological unexplained clinical conditions characterized by pain.



“The literature suggests considerable comorbidity between urological and nonurological unexplained clinical conditions. The most evidence for overlap, up to 79 percent, was between IBS and urological unexplained clinical conditions, particularly CPP.”

Maria Angeles Bullones Rodriguez

Department of Psychology,
University Rey Juan Carlos,
Madrid, Spain, and
colleagues

An article published in the November 2009 issue of the *Journal of Urology* focuses on the overlap of urological conditions such as chronic pelvic pain (CPP), interstitial cystitis (IC), painful bladder syndrome (PBS), chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and vulvodynia with nonurological conditions including fibromyalgia (FM), chronic fatigue syndrome (CFS), temporomandibular joint and muscle disorders (TMD), and irritable bowel syndrome (IBS). The research was funded by the NIDDK.

Maria Angeles Bullones Rodriguez, Department of Psychology, University Rey Juan Carlos, Madrid, Spain, and colleagues searched 12 databases using hallmark symptoms and syndromes as search terms. They identified and reviewed 1,037 full-length published articles in eight different languages that were published between 1966 and 2008. The articles included in this review examined the comorbidity or overlap of at least one urological condition or hallmark symptom with at least one nonurological condition or hallmark symptom.

“The literature suggests considerable comorbidity between urological and nonurological unexplained clinical conditions. The most evidence for overlap, up to 79 percent, was between IBS and urological unexplained clinical conditions, particularly CPP,” wrote Rodriguez and colleagues.

“This overlap may reflect publication bias or the anatomical fact that urological CPP conditions and IBS develop in a similar region of the body

and involve visceral pain sensations,” Rodriguez and colleagues stated in the journal publication. However, the findings generally support assertions of overlap among some or all of the urological and nonurological unexplained clinical conditions, the researchers added.

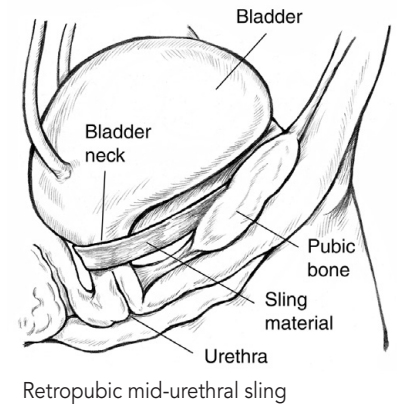
The few studies of FM, CFS, and TMD suggest a more modest comorbidity with urological unexplained clinical conditions. The article states that some experts argue the comorbidity of FM, CFS, TMD, and IBS could result from similarities in their case definitions. However, the researchers presented another viewpoint: “Although this explanation may apply to the overlap between urological pelvic pain conditions and IBS, urinary and pelvic pain symptoms are not part of the symptom criteria for FM, CFS, or TMD. Thus, commonalities in symptom criteria cannot completely account for the overlap we summarize.”

Concerning unexplained clinical conditions, the article states that despite decades of research, their etiology and pathophysiology remain elusive. The researchers identified three dominant perspectives on the mechanisms of these conditions. First, they cited physiological processes, including neuroendocrine, immunological, and neurotransmitter dysfunction in the central nervous system. Second, they cited victimization, abuse, and trauma. Third, they listed psychological distress, psychological disorders, stress

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Study Finds Two Sling Surgeries Equally Effective for Bladder Control in Women

Two common operations for stress urinary incontinence (SUI) help women achieve similar levels of dryness, according to a team of urologists and urogynecologists who compared the treatments in a large U.S. trial supported by the National Institutes of Health (NIH). The study was published in the June issue of *The New England Journal of Medicine* to coincide with a presentation at the annual meeting of the American College of Obstetrics and Gynecology.



"This rigorous, large-scale, comparative effectiveness trial represents a major milestone in treatment for stress urinary incontinence, an underdiagnosed public health problem affecting millions of American women."

Griffin P. Rodgers, M.D., M.A.C.P.
Director, NIDDK

The Trial of Mid-Urethral Slings (TOMUS) found that the two most common mid-urethral sling procedures are similar in their chance of cure, though each surgery has different risks. Mid-urethral slings are made of a synthetic mesh material that acts as a hammock, or sling, to support the urethra and prevent leakage. The urethra is the tube through which urine passes out of the body.

One of the mid-urethral sling procedures tested by this study is transobturator, meaning through the obturator area of the pelvis. It passes the sling material under the urethra and out through the upper inner thigh or groin area. The other procedure is retropubic, or behind the pubic bones of the pelvis. It passes a sling material under the urethra and behind the pubic bone.

Twelve months after surgery, women who received the transobturator mid-urethral sling and women who received the retropubic mid-urethral sling had equivalent levels of treatment success: 78 to 81 percent of women achieved dryness. Considering only self-reported dryness, 56 percent of women in the transobturator group and 62 percent of women in the retropubic group reported they had been cured, a small difference between the two groups that could have occurred by chance.

"This rigorous, large-scale, comparative effectiveness trial represents a major milestone in treatment for stress urinary incontinence, an underdiagnosed public health problem affecting millions of American women," said Griffin P. Rodgers, M.D., M.A.C.P., director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the NIH. "Investments in this kind of research enable women and their doctors to weigh more accurately the benefits and risks of available treatment options."

Women with SUI leak urine when coughing, laughing, sneezing, running, or lifting heavy objects. SUI is commonly treated with surgery designed to provide additional support to the bladder neck and urethra during increases in abdominal pressure that occur with activities. Mid-urethral sling surgeries are approved by the U.S. Food and Drug Administration and have been performed in the United States for more than a decade.

The study randomized 597 women with SUI to receive either a transobturator or retropubic mid-urethral sling. Complete information used to assess urinary incontinence was available for 95 percent of patients 12 months after surgery.

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Quality of life, patient satisfaction, and side effects were also studied. Most women in the study were satisfied with the results of treatment.

Each type of surgery has different risks and side effects. Serious adverse events were more common in the retropubic group (14 percent), compared with the transobturator group (6 percent). The retropubic group experienced more bladder perforations during surgery and serious voiding, or bladder emptying, problems requiring surgical correction, while the transobturator group experienced more vaginal perforations during surgery and neurological problems, such as weakness of the upper leg. Blood loss during surgery, duration of surgery, and likelihood of post-surgery urinary tract infections were all modestly higher in the retropubic group, compared with the transobturator group.

The study defined two types of treatment success. The surgery was deemed an objective success if participants had no leakage during a stress test and a 24-hour pad test, and they required no additional treatment for the problem. Women also reported leakage using validated questionnaires and a 3-day voiding diary and reported additional treatment, such as surgery, behavioral therapy, or drug therapy. Negative results on all of these measures meant the surgery was a subjective success.

Overall, subjective self-reported treatment success was lower than objective success, a common finding among scientific studies of urinary incontinence. Cure rates in this clinical trial were lower than in previous studies, likely because participants had to test negative on several measures, rather than just one. Similar to previous studies of urinary incontinence, researchers found that women with more severe urethral dysfunction were no more likely to fail with the transobturator sling than with the retropubic sling.

The NIDDK, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the Office of Research on Women's Health fund the Urinary Incontinence Treatment Network (UITN), a group of nine clinical centers and a biostatistical center. The UITN conducts rigorous, long-term clinical trials of common therapies for incontinence. The Office of Research on Women's Health also provides support for extended follow-up of the women enrolled in the study to observe the long-term effects of these surgeries.

"Patient-reported treatment success combined with clinical measures of success gives us clear evidence about the comparative effectiveness of these two procedures and the risks associated with each approach," said Robert A. Star, M.D., director of the Division of Kidney, Urologic, and Hematologic Diseases at the NIDDK. "The study also highlights potential complications that doctors and patients need to discuss before surgery."

Many urinary incontinence studies predating the UITN study were small, short-term, or less stringent about diagnostic criteria and outcome measures, producing inconsistent results across studies. The UITN study set a higher bar by standardizing definitions, clinical evaluations, and surgical procedures at all sites and by using many measures of treatment success, which may increase the applicability of study results to patients who did not participate in the study. Prior to this study, few clinical trials had been conducted to compare these operations for both likelihood of treatment success and risks.

Urinary incontinence is a common and costly condition that results in poorer quality of life for women. Another study funded by the NIH reports that approximately half of American



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NIH and FDA Announce Partnership to Speed New Treatments to Patients

The U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have launched an initiative designed to accelerate the process from scientific breakthrough to the availability of new, innovative medical therapies for patients. The collaboration combines the NIH's vast experience supporting and facilitating new discoveries in the laboratory and clinic with the FDA's more than 100 years of experience and knowledge in the regulation and approval of drugs, biologics, and medical devices.



"Collaboration between NIH and FDA, including support for regulatory science, will go a long way to foster access to the safest and most effective therapies for the American people."

Kathleen Sebelius
Secretary, U.S. Department of
Health and Human Services

The initiative involves two interrelated scientific disciplines: translational science, the shaping of basic scientific discoveries into treatments, and regulatory science, the development and use of new tools, standards, and approaches to more efficiently develop products and more effectively evaluate product safety, efficacy, and quality. Both disciplines are needed to turn biomedical discoveries into safe and beneficial treatments.

The agencies will establish a Joint NIH–FDA Leadership Council to spearhead collaborative work on important public health issues. The Joint Leadership Council's work will help ensure that regulatory considerations form an integral component of biomedical research planning and that the latest science is integrated into the regulatory review process.

In addition, the NIH and the FDA will jointly issue a Request for Applications, making \$6.75 million available over 3 years for work in regulatory science. The research supported

through this initiative should add to the scientific knowledge base by providing new methods, models, or technologies that will inform the scientific and regulatory community about better approaches to evaluating safety and efficacy in medical product development.

"We've all been following the remarkable advances in biomedical sciences led by the NIH with great enthusiasm for years," said U.S. Department of Health and Human Services Secretary Kathleen Sebelius, who announced the initiative on February 24, 2010. "However, much more can be done to speed the progress from new scientific discoveries to treatments for patients. Collaboration between NIH and FDA, including support for regulatory science, will go a long way to foster access to the safest and most effective therapies for the American people."

For more information about the NIH and FDA initiative, please visit www.nih.gov/news/health/feb2010/od-24.htm. ■

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Expenditures and Results (RePORTER) tool located at www.projectreporter.nih.gov/reporter.cfm. The research described in this article is funded under NIDDK grant number 5K23DK078671–02.

The National Kidney and Urologic Diseases Information Clearinghouse, an information dissemination service of the NIDDK, has fact sheets and easy-to-read booklets about urological diseases. For more information and to obtain copies, visit www.urologic.niddk.nih.gov. ■

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tolerance, and stress recovery. In some cases, affected patients did not have symptoms from any of the three dominant perspectives. Therefore, a multidimensional conceptual model seems better suited to guide research and understanding of these conditions and co-occurrence.

The authors argued that a more broadly based conceptual model can better investigate etiology, clinical manifestations, comorbidity, and prognosis. Examining pain, which is prominent across the syndromes of interest, is crucial to understanding their substantial comorbidity.

The researchers stated that although comorbidity was shown, earlier studies have several methodological shortcomings that undermine the strength of the conclusion and limit comparability across studies. The researchers also asserted that future studies should adhere to the established research diagnostic criteria for each

condition, and longitudinal cohort designs are needed to examine risk factors, temporal onset, and prognosis. These well-controlled studies will advance the understanding of and improve treatment for these conditions.

More information about research projects funded by the National Institutes of Health can be found by using the Research Portfolio Online Reporting Tools (RePORT) Expenditures and Results (RePORTER) tool located at www.projectreporter.nih.gov/reporter.cfm. The research described in this article is funded under NIDDK grant number 3U01DK082325-02S1.

The National Kidney and Urologic Diseases Information Clearinghouse, an information dissemination service of the NIDDK, has fact sheets and easy-to-read booklets about CPP, IC, PBS, and CP/CPPS. For more information and to obtain copies, visit www.urologic.niddk.nih.gov. ■

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women have some degree of urinary incontinence, and the direct cost of incontinence for women was \$12.4 billion in 1995, the last year for which national estimates are available.

The TOMUS is the third in a series of clinical trials completed by the UITN. The first, the Stress Incontinence Surgical Treatment Efficacy Trial, compared two older, gold standard surgeries for SUI. More about those results is available at www.nih.gov/news/pr/may2007/niddk-21.htm. The second trial, the Behavior Enhances Drug Reduction of Incontinence, asked women to make behavioral changes such as emptying the bladder on a regular schedule and practicing pelvic muscle exercises, known as Kegel exercises, to strengthen pelvic muscles to determine if these common treatments would allow women to stop drug therapy and maintain the same degree of bladder control. More information is available at www.springerlink.com/content/tj7272157274k833.

More information about research projects funded by the NIH can be found by using the Research Portfolio Online Reporting Tools (RePORT) Expenditures and Results (RePORTER) tool located at www.projectreporter.nih.gov/reporter.cfm. The research described in this article is funded under NIDDK grant number 5U01DK060395-08. The direct link to the project is www.projectreporter.nih.gov/project_info_description.cfm?aid=7686867&icde=3850292.

For a list of centers enrolling patients for urinary incontinence trials, visit www.uitn.net or search for urinary incontinence at www.ClinicalTrials.gov, where the TOMUS study is registered as NCT00325039.

For materials from the NIDDK about bladder control for women, visit www.kidney.niddk.nih.gov/kudiseases/pubs/bladdercontrol. ■

NIDDK Celebrates 60 Years of Research to Improve Health



"We celebrate the Institute's accomplishments over the past 60 years in supporting and conducting research on some of the most common, chronic, and costly diseases affecting people in this country and around the world."

Griffin P. Rodgers, M.D., M.A.C.P.
Director, NIDDK

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) was established 60 years ago by President

Harry S. Truman. In announcing activities that will mark the Institute's anniversary, NIDDK Director Griffin P. Rodgers, M.D., M.A.C.P., said, "We celebrate the Institute's accomplishments over the past 60 years in supporting and conducting research on some of the most common, chronic, and costly diseases affecting people in this country and around the world, as well as on diseases and disorders that are less widespread but nonetheless devastating in their impacts."

As part of the commemoration of the NIDDK's 60th anniversary, the Institute published *NIDDK: 60 Years of Advancing Research to Improve Health*, which highlights the Institute's research accomplishments and describes its current efforts and future plans. The publication is available to read or download at www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/SixtiethAnniversary. A video highlighting select advances from the 60th anniversary publication is available at www3.niddk.nih.gov/video/60_anniv.



The NIDDK also has announced a schedule of special events to commemorate the anniversary. Among these activities is the NIDDK's scientific symposium "Unlocking the Secrets of Science: Building the Foundation for Future Advances," which will be held in Bethesda, MD, on September 21, 2010. More information about this and other activities is available at www2.niddk.nih.gov/60thAnniversaryEvents.htm. ■

NIDDK Information Products Receive 14 Plain Language Awards

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) publications, websites, and other informational products have been honored with 14 National Institutes of Health (NIH) Plain Language Awards. The annual awards program, now in its 10th year, honors communication products that help the NIH reach all Americans with health information they can use and research results they can easily understand.

NIDDK resources—including publications, radio reports, and web-based materials—received five Bronze, five Silver, and four Gold awards. The winning publications included easy-to-read materials designed for Spanish- and Vietnamese-speaking audiences.

More than 300 nominations were submitted for this year's awards, and the winners were announced during a ceremony May 26. Information about the NIH Plain Language Awards program and a list of winning entries is available at www.nih.gov/clearcommunication/plainlanguage.htm. ■

NIDDK Scientist Elected to American Academy of Arts and Sciences

G. Marius Clore, M.D., Ph.D., chief of the National Institute of Diabetes and Digestive and Kidney Diseases' Protein Nuclear Magnetic Resonance Section, was elected a member of the American Academy of Arts and Sciences. Each year the Academy, founded in 1780, elects a class of men and women of exceptional achievement in science, scholarship, business, public affairs, and the arts to conduct projects and studies responsive to society's needs and problems. Visit www.amacad.org to learn more about the Academy. ■



NIDDK Publication Highlights Research Advances



NIDDK Recent Advances and Emerging Opportunities, published each year since 2001, provides examples of the research advances made by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded scientists and their colleagues in the most recent fiscal year. The 2010 publication includes "Stories of Discovery," which traces progress in specific research areas, and "Patient Profiles," which tells patients' personal stories. The publication is available to read or download at www2.niddk.nih.gov/AboutNIDDK/ResearchAndPlanning/Advances/FY2010/default.htm. ■

Would you like to know more about NIDDK-supported research?

The National Institutes of Health (NIH) provides access to a variety of reporting tools, reports, data, and analyses of NIH research activities at the Research Portfolio Online Reporting Tools (RePORT) website, www.projectreporter.nih.gov/reporter.cfm. One of the tools available is RePORT Expenditures and Results (RePORTER), which allows users to search a repository of NIH-funded research projects and access and download publications and patents resulting from NIH funding. ■

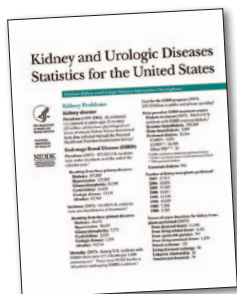
Additional Resources

Updated Publication

The National Kidney and Urologic Diseases Information Clearinghouse has updated the following publication:

- *Kidney and Urologic Diseases Statistics for the United States*

The publication is available at www.urologic.niddk.nih.gov.



Interactive Tools

New to the Interactive Health Education Tools section of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website is a videocast titled “NIDDK Video Web Tour.”

The NIDDK interactive tools section consolidates tools and resources about urologic diseases from the National Institutes of Health and the National Library of Medicine. To access these resources, visit www.kidney.niddk.nih.gov/resources/HealthTools. ■

Upcoming Meetings, Workshops, and Conferences

The National Institute of Diabetes and Digestive and Kidney Diseases Information Clearinghouses will exhibit at the following upcoming event:

American Society of Nephrology Renal Week 2010

November 16–21 in Denver.

For more information, visit www.asn-online.org. ■